1 575 800

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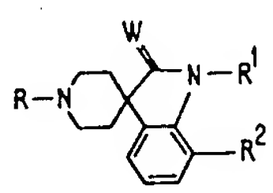
(54) SPIRO AMINES, THEIR PRODUCTION AND COMPOSITIONS CONTAINING THEM

(71) We, SUMITOMO CHEMICAL COMPANY LIMITED, a corporation organized under the laws of Japan, of 15, Kitahama-5-chome, Higashi-ku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is performed, to be particularly described in and by the following statement:-

The present invention relates to spiro amine derivatives having antihypertensive activity and central nervous system depressant activity, and to the preparation and use thereof.

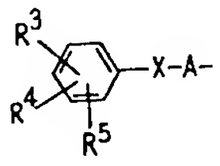
More particularly, the present invention provides a spiro amine derivative of the general formula:



(I)

Wherein R^1 is a hydrogen atom, a C_1 - C_4 alkyl group, a phenyl group which is unsubstituted or substituted by a halogen atom, a C_1 - C_4 alkyl group or a C_1 - C_4 alkoxy group, R^2 is absent or R^1 and R^2 together, form a C_1 - C_4 alkylene radical and thus together with the indolene nucleus define a ring, W is an oxygen atom or two hydrogen atoms and R is a group of the formula:

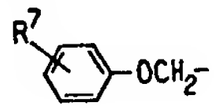
(a)



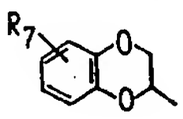
(wherein A is a C_1 - C_4 alkylene, X is absent or is a carbonyl group, an oxygen atom, the radical $\rangle$CH-OH or the radical -CG=CH- and R^3, R^4 and R^5 are each optionally present and are each, independently of one another, a C_1 - C_4 alkyl group, a C_1 - C_4 alkoxy group, a- benzyloxy group, a halogen atom or a hydroxy group) or

(b) R^6-CHCH$_2$-
|
OH

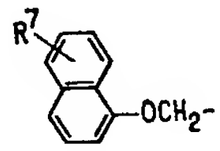
(wherein R^6 is a group of the formula:

(i) 

(wherein R^7 is optionally present and is a halogen atom, a cyano group, a C_1 - C_4 alkyl group, a C_1 - C_4 alkoxy group or a hydroxyl group),



(wherein R^7 is as defined above) or

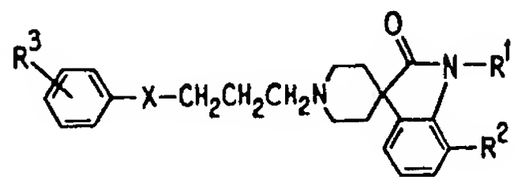
(ii) 

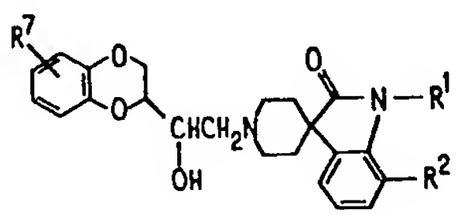
(wherein R^7 is as defined above)), or a pharmaceutically acceptable salt, e.g. an acid addition or quaternary ammonium salt, thereof.

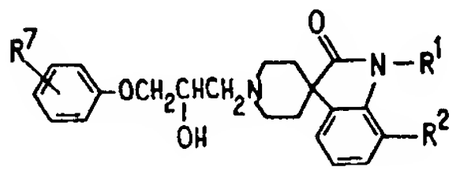
The "halogen" atom may be chlorine, fluorine, bromine or iodine; the C_1 - C_4 alkyl group may be a straight or branched chain alkyl group having from one to four carbon atoms inclusive (e.g. methyl, ethyl, isopropyl or butyl): the C_1 - C_4 alkoxy group is an alkoxy group having from one to four carbon atoms inclusive (e.g. methoxy, ethoxy or isopropoxy); the C_1 - C_4 alkylene radical may be methylene, ethylene, trimethylene or tetramethylene.

We have found that spiro amine derivatives within the formula (I) as defined above have a hypotensive activity and are useful as anti-hypertensive agents. They also have a central nervous system depressant activity and are useful as transuqillizers and anti-psychotic agents.

Among the spiro amine derivatives of the formula (I) the preferred compounds are those in which W is an oxygen atom. Furthermore, particularly preferred compounds are those within any of the formulae:



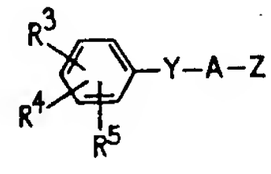




wherein R^1, R^2, R^3 and R^7 are each as defined above, and X is a carbonyl group or the radical -CH-OH.

For example, 1'-(3-(4-fluorobenzoyl)propyl)-1-methyl-2-oxo-indoline-3-spiro-4'-piperidine has a potent hypotensive activity at low dosages (0.1 mg/kg - 0.3 mg/kg ip).

In a process within the present invention, a spiro amine derivative of the formula (I) is prepared by reacting a compound of the formula:

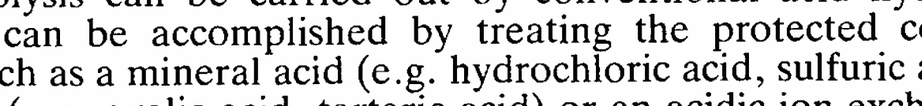
 (II)

wherein Y is absent or is a carbonyl group, a protected carbonyl group, an oxygen atom, the radical $>$CH-OH or the radical -CH=CH-, Z is a halogen atom and A, R^3, R^4 and R^5 are

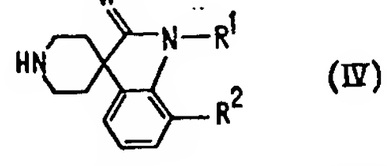
as defined above, or a compound of the formula:

$$R^6 - B \qquad \text{(III)}$$

wherein R^6 is as defined above and B is a group of the formula:



(wherein Z is as defined above) with a spiro amine derivative of the formula:



(IV)

wherein R^1, R^2 and W are each as defined above, optionally followed by reduction of a carbonyl group, or by hydrolysis of a protected carbonyl group, and optionally salifying the resultant product.

A spiro amine derivative in which R^3, R^4 or R^5 is a hydroxy group can also be prepared by debenzylation of the corresponding benzyloxy derivative.

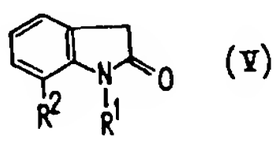
The condensation reaction is usually carried out in an inert solvent such as an aromatic hydrocarbon (e.g. benzene, toluene, xylene), an amide (e.g. dimethyl-formamide, N,N-dimethylacetamide), an ether (e.g. dioxane, tetrahydrofuran), an alcohol (e.g. ethanol, n-butanol, propanol, amyl alcohol), an alkanone (e.g. acetone, butanone, methyl isobutyl ketone) or dimethyl sulfoxide at a temperature within a range of from 0°C to the boiling point of the solvent inclusive. Preferably, a basic substance such as an alkali metal hydrogen carbonate (e.g. sodium hydrogen carbonate, potassium hydrogen carbonate), an akali metal carbonate (e.g. sodium carbonate, potassium carbonate), an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide) or an organic amine (e.g. pyridine, triethylamine) is used as an acid binding agent. A small amount of a reaction accelerating agent such as potassium iodide may also be added.

The hydrolysis can be carried out by conventional acid hydrolyzing procedure. For instance, it can be accomplished by treating the protected compound with an acidic substance such as a mineral acid (e.g. hydrochloric acid, sulfuric acid, phosphoric acid), an organic acid (e.g. oxalic acid, tartaric acid) or an acidic ion exchange resin in water or an alkanol (e.g. methanol, ethanol, propanol), usually under mild conditions, e.g. at room temperature. Further, it may be accelerated by elevation of the temperature.

The reduction of a carbonyl group can be carried out in an inert solvent such as an ether (e.g. diethyl ether, tetrahydrofuran, dioxane), an alcohol (e.g. methanol, ethanol, isopropanol), benzene, toluene or water at a temperature within a range of from room temperature to the boiling point of the solvent.

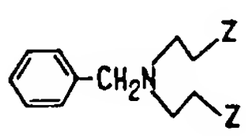
Suitable reducing agents which are preferably employed in the reaction are metal hydride complexes such as lithium aluminium hydride, sodium borohydride, bis-(2-methoxyethoxy) aluminium chloride or sodium aluminium diethyl dihydride, palladium on charcoal or platinum oxide.

A spiro amine derivative of the formula (IV) can be prepared by condensation of an oxoindole derivative of the formula:



(V)

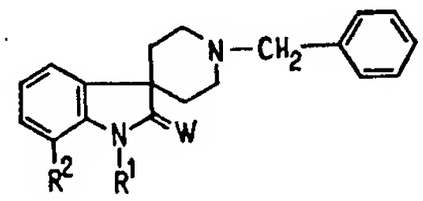
wherein R^1 and R^2 are each as defined above with a dihalide of the formula:



(VI)

wherein Z is as defined above, optionally followed by reduction of an amide group to give a

compound of the formula:

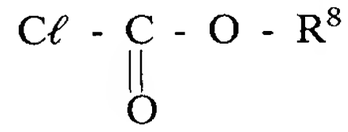


(VII)

wherein R^1, R^2 and W are each as defined above, followed, by debenzylation of the latter.

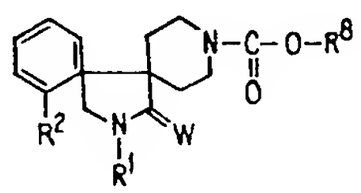
The condensation reaction of the compound (V) with the compound (VI) can be carried out in an inert solvent such as an aromatic hydrocarbon (e.g. benzene, toluene, xylene) at temperature with a range of from room temperature to the boiling point of the solvent inclusive. A suitable condensation agent is a metal hydride (e.g. sodium hydride, calcium hydride), metal alkoxide (e.g. sodium ethoxide, potassium t-butoxide) or sodium amide.

The debenzylation can be carried out by a conventional catalytic hydrogenation procedure, or by treating the compound (VII) with a compound of the formula:



(VIII)

wherein R^8 is a C_1 - C_4 alkyl group or a benzyl group followed by hydrolysis or hydrogenolysis of the compound of the formula:

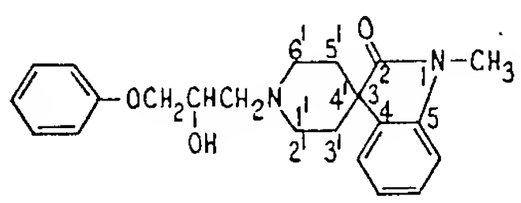


(IX)

wherein R^1, R^2, W and R^8 are each as defined above.

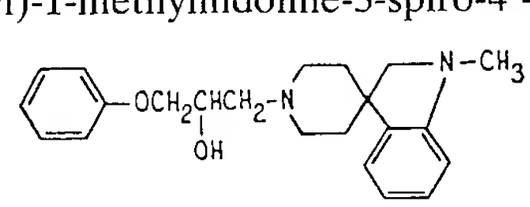
Specific examples of spiro amine derivatives within the formula (I) are as follows:

1′-(2-hydroxy-3-phenoxypropyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

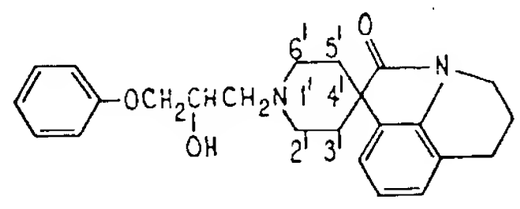


1′-(2-hydroxy-3-phenoxypropyl)-1-ethyl-2-oxo-indoline-3-spiro-4′-piperidine

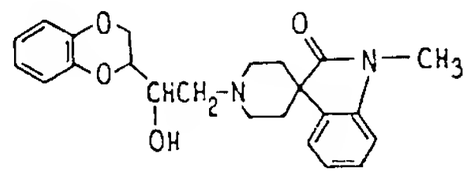
1′-(2-hydroxy-3-phenoxypropyl)-1-methylindoline-3-spiro-4′-piperidine



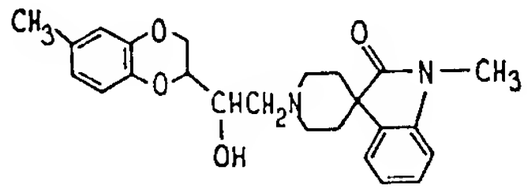
1′-(2-hydroxy-3-phenoxypropyl)-2-oxo-1,2,5,6-tetrahydro-4*H*-pyrrolo (3,2,1 ij)quinoline-1-spiro-4′-piperidine



1′(2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

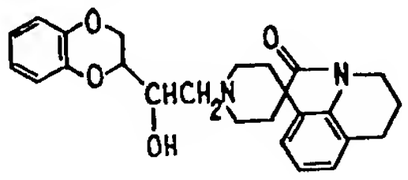


1′-(2-(6-methyl-1,4-benzodioxan-2-yl)-2-hydroxy-ethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine



1′-(2-(6-methoxy-1,4-bensodioxan-2-yl)-2-hydroxyethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-(1,4-bensodioxan-2-yl)-2-hydroxyethyl)-2-oxo-1,2,5,6-tetrahydro-4*H*-pyrrolo(3,2,1-ij) quinoline-1-spiro-4′-piperidine



1′-(2-hydroxy-3-(1-naphthyloxy)propyl)-2-oxo-1,2,5,6-tetrahydro-4*H*-pyrrolo (3,2,1-ij)quinoline-1-spiro-4′-piperidine

1′-(2-hydroxy-3-(1-naphthyloxy)propyl)-1-ethyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl)-1-propyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl)-1-ethyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl)-1-methylindoline-3-spiro-4′-piperidine

1′-(2-hydroxy-3-(2-chlorophenoxy)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-hydroxy-3-(2-methylphenoxy)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-hydroxy-3-(2-methoxyphenoxy)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

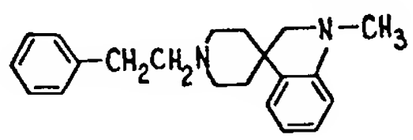
1′-(2-hydroxy-3-(2-cyano-phenoxy)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl)-1-phenyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-hydroxy-3-(1-naphthyloxy)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-hydroxy-3-(1-naphthyloxy)propyl)-1-ethyl-indoline-3-spiro-4′-piperidine

1′-(2-phenylethyl)-1-methylindoline-3-spiro-4′-piperidine



1′-(3-(4-fluorobenzoyl)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(3-(4-fluorobenzoyl)propyl)-1-ethyyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(3-(4-fluorobenzoyl)propyl)-1-propyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(3-(4-fluorobenzoyl)propyl)-1-phenyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(3-(4-fluorobenzoyl)propyl)-1-methylindoline-3-spiro-4′-piperidine

1′-(3-(4-fluorobenzoyl)propyl)-1-ethyl-indoline-3-spiro-4′-piperidine

1′-(4-(4-fluorophenyl)-4-hydroxybutyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(3-(3,4-dimethoxybenzoyl)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(3-(4-methoxybenzoyl)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(4-(3,4,5-trimethoxyphenyl)-4-hydroxybutyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-phenoxyethyl)-1-ethyl-indoline-3-spiro-4′-piperidine

1′-(2-(4-benzyloxyphenyl)-2-hydroxy-1-methylethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-(4-hydroxyphenyl)-2-hydroxy-1-methylethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

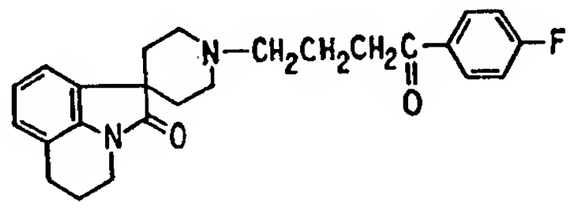
1′-(2-(4-fluorobenzoyl)ethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(3-phenylprop-2-ene-1-)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(2-benzoylpropyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

1′-(3-(4-fluorobenzoyl)propyl)-2-oxo-1, 2,5,6-tetrahydro-4*H*-pyrrolo(3,2,1-ij)quinoline-

1-spiro-4′-piperidine



1′-(4-(4-fluorophenyl)-4-hydroxybutyl)-2-oxo-1,2,5,6-tetrahydro-4H-pyrrolo(3,2,1-ij) quinoline-1-spiro-4′-piperidine

1′-(3-(4-fluorobenzoyl)propyl)-1,2,5,6-tetrahydro-4*H*-pyrrolo(3,2,1-ij)quinoline-1-spiro-4′-piperidine

1′-benzoylmethyl)-1,2,5,6-tetrahydro-4*H*-pyrrolo-(3,2,1-ij) quinoline-1-spiro-4′-piperidine

1′-(2-phenyl-2-hydroxyethyl)-1,2,5,6-tetrahydro-4*H*-pyrrolo(3,2,1-ij) quinoline-1-spiro-4′-piperidine

1′-(3-phenoxy-propyl)-1,2,5,6-tetrahydro-4*H*-pyrrolo(3,2,1-ij) quinoline-1-spiro-4′-piperidine

1′-(2-phenylethyl-1,2,5,6-tetrahydro-4*H*-pyrrolo-(3,2,1-ij)quinoline-1-spiro-4′-piperidine

1′-(3-(3,4-dimethylbenzoyl)propyl)-1-ethyl-indoline-3-spiro-4′-piperidine

Spiro amine derivatives within the formula (I) in the free base form can be converted into their pharmaceutically acceptable salts such as acid addition salts or quaternary ammonium salts by treatment with mineral acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid), organic acids (e.g. acetic acid, citric acid, oxalic acid, lactic acid, succinic acid, tartaric acid, cinnamic acid, ascorbic acid), alkyl halides or aralkyl halides.

Spiro amine derivatives within the formula (I) may be brought into a form suitable for administration by known methods.

The present invention additionally provides a pharmaceutical composition comprising at least one compound of the formula (I) or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable diluent or carrier.

For the preparation of such a pharmaceutical composition, a compound within the formula (I) may be mixed with a carrier or diluent such as water, sesame oil, calcium phosphate, starch, talcum, casein, magnesium stearate, methyl cellulose, a polyglycol or tragacanth, sometimes together with a stabilizer and/or emulsifying agent.

The resulting mixture may be processed in a conventional manner to produce, for example, tablets, capsules, pills and ampoules. The usual oral dosage is 1.0 - 500 mg per os daily.

Practical and preferred processes embodying the present invention are illustratively shown in the following Examples.

Example 1

A mixture of 3.0 g of 4-chloro-1-(4-fluoro-phenyl)-1-,1-ethylenedioxybutane, 2.0 g of 1-methyl-2-oxo-indoline-3-spiro-4′-piperidine, 2.8 g of anhydrous potassium carbonate, 0.1 g of potassium iodide and 30 ml of dimethylformamide was refluxed for 2 hours. The resulting mixture was poured into water and was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated in vacuo. To the residual oil were added 60 ml of methanol, 20 ml of water and 10 ml of concentrated hydrochloric acid. The mixture was refluxed for 25 minutes and concentrated in vacuo. The residual oil was made alkaline with 28% aqueous ammonia and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated. The residual oil was chromatographed over silica gel with ethyl acetate as an elueting agent to give 1′-(3-(4-fluorobenzoyl)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine, M.P. 95° - 96.5°C.

Example 2

In the same manner as that described in Example 1, the following compounds were obtained:

1′-(3-(4-methoxybenzoyl)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine
M.P. 75° - 79.5°C

1′-(3-(3,4-dimethoxybenzoyl)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine
M.P. 109° - 112°C

1′-(3-(4-fluorobenzoyl)propyl)-1-ethyl-2-oxo-indoline-3-spiro-4′-piperidine
M.P. 104° - 107°C

1′-(3-(4-fluorobenzoyl)propyl)-1-propyl-2-oxo-indoline-3-spiro-4′-piperidine
M.P. 90° - 91°C

1′-(3-(4-fluorobenzoyl)propyl)-1-methyl-indoline-3-spiro-4′-piperidine
M.P. 98° - 103°C

1′-(3-(4-fluorobenzoyl)propyl)-1-ethyl-indoline-3-spiro-4′-piperidine dihydrochloride
M.P. 214° - 216°C

1′-(3-(4-fluorobenzoyl)propyl)-1-phenyl-2-oxo-indoline-3-spiro-4′-piperidine
M.P. 116.5° - 117°C

1′-(3-(4-fluorobenzoyl)propyl)-2-oxo-1,2,5,6-tetrahydro-4*H*-pyrrolo(3,2,1-ij)quinoline-1-spiro-4′-piperidine
M.P. 105° - 109°C

1′-(3-(4-fluorobenzoyl)propyl)-1,2,5,6-tetrahydro-4*H*-pyrrolo(3,2,1-ij)quinoline-1-spiro-4′-piperidine dihydrochloride
M.P. 248° - 249°C

Example 3

A mixture of 1.63 g of 2-phenoxyethyl chloride, 1.5 g of 1-methyl-2-oxo-indoline-3-spiro-4′-piperidine, 1.44 g of anhydrous potassium carbonate, 0.1 g of potassium iodide and 30 ml of dimethylformamide was stirred at 90° - 100°C for 5 hours. The resulting mixture was poured into water and was extracted with diethylether. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The oil thus obtained was treated with hydrochloric acid to give 1′-(2-phenoxyethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine hydrochloride
M.P. 206° - 210°C

Example 4

In the same manner as that described in Example 3, the following compounds were obtained:

1′-cinnamyl-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine hydrochloride
M.P. 252° - 255°C

1′-(2-phenylethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine hydrochloride
M.P. 167.5° - 169°C

1′-(2-phenylethyl)-1-methyl-indoline-3-spiro-4′-piperidine dihydrochloride
M.P. > 280°C

1′-(2-phenylethyl)-1-phenyl-2-oxo-indoline-3-spiro-4′-piperidine hydrochloride
M.P. 128° - 137°C

1′-(2-(4-fluorobenzoyl)ethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine hydrochloride
M.P. 196° - 200°C

Example 5

A mixture of 0.4 g of 1′-(3-(4-fluorobenzoyl)-propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine, 1.0 g of sodium borohydride and 20 ml of isopropyl alcohol was refluxed for 30 minutes.

The resulting mixture was poured into water and was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residual solid was washed with diisopropylether to give 1′-(4-(4-fluorophenyl)-4-hydroxy-butyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine
M.P. 126.5° - 127.5°C

Example 6

In the same manner as that described in Example 5, the following compounds were obtained:

1′-(4-(4-fluorophenyl)-4-hydroxybutyl)-2-oxo-1,2,5-6-tetrahydro-4*H*-pyrrolo(3,2,1-ij)quinoline-1-spiro-4′-piperidine
M.P. 137° - 141°C

1′-(4-(3,4-dimethoxyphenyl)-4-hydroxybutyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine
M.P. 114° - 122°C

1′-(4-(4-fluorophenyl)-4-hydroxybutyl)-1-ethyl-2-oxo-indoline-3-spiro-4′-piperidine
M.P. 131° - 134°C

Example 7

A mixture of 3.8 g of *p*-benzyloxy-α-bromopropiophenone, 2 g of 1-methyl-2-oxo-indoline-3-spiro-4′-piperidine, 2 g of sodium bicarbonate and 30 ml of dimethyl-formamide was stirred for 5 hours at room temperature.

The resulting mixture was poured into water and was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The oil thus obtained was washed with n-hexane to give 1′-(1-(4-benzyloxybenzoyl)ethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

IR $\nu_{C=0}$ 1680 - 1710 cm^{-1}

Example 8

A mixture of 4.5 g of 1′-(1-(4-benzyloxybenzoyl)-ethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine, 5.6 of sodium borohydride and 150 ml of isopropyl alcohol was refluxed for 1 hour. The resulting mixture was poured into water and was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude solid was recrystallized from ethanol to give 1′-(2-(4-benzyloxy-phenyl)-2-hydroxy-1-methylethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine.

M.P. 195° - 199°C

The mother liquor was concentrated *in vacuo* and was chromatographed over silica gel to give the isomer.

M.P. 93.5° - 98.5°C

Example 9

A mixture of 0.7 g of 1′-(2-(4-benzyloxyphenyl)-2-hydroxy-1-methylethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine (melting point 195° - 199°C), 0.1 g of 10% palladium on charcoal and 120 ml of ethanol was vigorously stirred under atmospheric hydrogen at room temperature, until an equimolar amount of hydrogen was consumed. The catalyst was filtered off, and the filtrate was concentrated in vacuo.

The solid thus obtained was washed with diisopropyl ether to give 1′-(2-(4-hydroxyphenyl)-2-hydroxy-1-methylethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

M.P. 223° - 225°C

Example 10

A mixture of 1.7 g of 1-phenoxy-2, 3-epoxypropane, 2 g of 1-methyl-2-oxo-indoline-3-spiro-4′-piperidine and 120 ml of ethanol was refluxed for 3 hours. The resulting mixture was concentrated and crystallized from diisopropyl-ether to give 1′-(2-hydroxy-3-phenoxypropyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

M.P. 104° - 110°C

Example 11

In the same manner as that described in Example 10, the following compounds were obtained:

1′-(2-hydroxy-3-(1-naphthyloxy)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

M.P. 148.5° - 150.5°C

1′-(2-hydroxy-3-(1-naphthyloxy)propyl)-2-oxo-1,2,5,6-tetrahydro-4H-pyrrolo(3,2,1-ij)quinoline-1-spiro-4′-piperidine

M.P. 113° - 119°C

1′-(2-hydroxy-3-(1-naphthyloxy)-propyl)-1-ethyl-indoline-3-spiro-4′-piperidine

M.P. 114° - 118°C

Example 12

A mixture of 2.9 g of 1-(1,4-benzodioxan-2-yl)-2-bromoethanol, 2 g of 1-methyl-2-oxo-indoline-3-spiro-4′-piperidine, 1.9 g of sodium carbonate and 30 ml of dimethylformamide was stirred for 1.5 hours at 100 °C. The resulting mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*.

The residual oil was chromatographed over silica gel and washed with diisopropylether to give 1′ -(2-(1,4-benzodioxan-2-yl)2-hydroxyethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine

M.P. 113° - 128°C

Example 13

In the same manner as that described in Example 12, 1′-(2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl)-2-oxo-1,2,5,6-tetrahydro-4H-pyrrolo(3,2,1-ij)quinoline-1-spiro-4′-piperidine was obtained.

M.P. 197° - 207°C

Reference Example

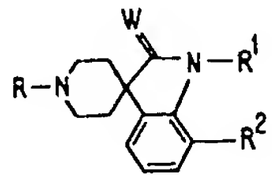
A mixture of 15.1 g of 1′-benzyl-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine, 33.5 g of benzyloxy-carbonyl chloride and 530 ml of toluene was refluxed for 6 hours. The resulting mixture was poured into water and extracted with ethylacetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The oil thus obtained was washed with n-hexane to give 1′-benzyloxycarbonyl-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine.

A mixture of 12 g of the solid thus obtained, 21.6 g of water, 7.2 g of 5% palladium on charcoal and 500 ml of ethanol was vigorously stirred under atmospheric hydrogen at room temperature, until the reaction was complete. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The solid thus obtained was washed with diisopropylether to give 1-methyl-2-oxo-indoline-3-spiro-4′-piperidine.

M.P. 146° - 151°C

WHAT WE CLAIM IS:-

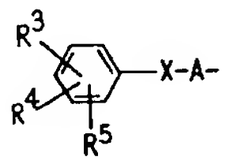
1. A compound of the formula



(I)

wherein R^1 is a hydrogen atom, a C_1 - C_4 alkyl group, a phenyl group which is unsubstituted or substituted by a halogen atom, a C_1 - C_4 alkyl group or a C_1 - C_4 alkoxy group, R^2 is absent or R^1 and R^2 together form a C_1 - C_4 alkylene radical and thus together with the indoline nucleus define a ring, W is an oxygen atom or two hydrogen atoms and R is a group of the formula:

(a)

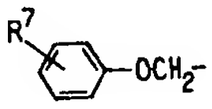


(wherein A is a C_1 - C_4 alkylene, X is absent or is a carbonyl group, an oxygen atom, the radical >CH-OH or the radical -CH=CH- and R^3, R^4 and R^5 are each optionally present and are each, independently of one another, a C_1 - C_4 alkyl group, a C_1 - C_4 alkoxy group, a benzyloxy group, a halogen atom or a hydroxy group) or

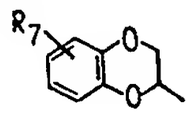
(b) R^6-CH(OH)-CH_2-

(wherein R^6 is a group of the formula:

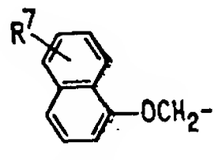
(i)



(wherein R^7 is optionally present and is a halogen atom, a cyano group, a C_1 - C_4 alkyl group, a C_1 - C_4 alkoxy group or a hydroxy group),

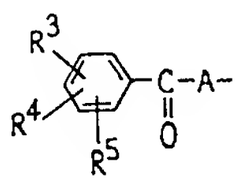
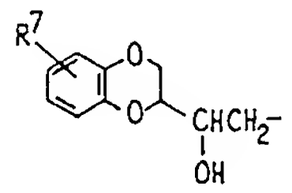


(wherein R^7 is as defined above) or



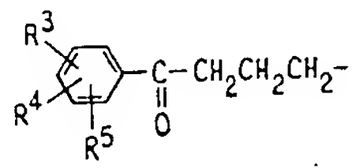
(wherein R^7 is as defined above)), or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein W is an oxygen atom.
3. A compound according to Claim 1, wherein R is a group of the formula:


or


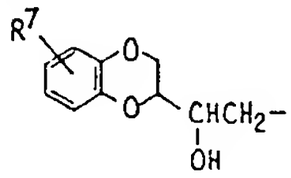
(wherein R^3, R^4, R^5, A and R^7 are each as defined in Claim 1).

4. The compound according to Claim 1, wherein W is an oxygen atom and R is a group of the formula:



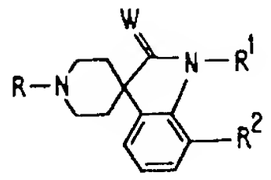
(wherein R^3, R^4 and R^5 are each as defined in Claim 1).

5. A compound according to Claim 1, wherein W is an oxygen atom and R is a group of the formula:

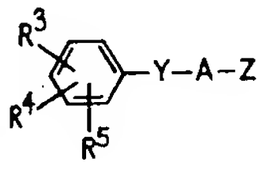


(wherein R^7 is as defined in Claim 1).

6. 1′-(3-(4-fluorobenzoyl)propyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine.
7. 1′-(3-(4-fluorobenzoyl)propyl)-1-propyl-2-oxo-indoline-3-spiro-4′-piperidine.
8. 1′-(2-hydroxy-3-phenoxypropyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine.
9. 1′-(3-(4-fluorobenzoyl)propyl)-2-oxo-1,2,5,6-tetrahydro-4*H*-pyrrolo(3,2,1-ij)quinoline-1-spiro-4′-piperidine.
10. 1′-(2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl)-1-methyl-2-oxo-indoline-3-spiro-4′-piperidine.
11. 1′-(2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl)-2-oxo-1,2,5,6-tetrahydro-4*H*-pyrrolo(3,2,1-ij)quinoline-1-spiro-4′-piperidine.
12. A process for producing a spiro amine derivative of the formula:



wherein R, R^1, R^2, and W are each as defined in Claim 1, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of the formula:

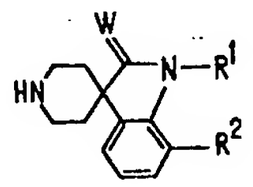


wherein R^3, R^4, R^5 and A are each as defined in Claim 1, Z is a halogen atom and Y is absent or is a carbonyl group, a protected carbonyl group, an oxygen atom, the radical >CH-OH or the radical -CH=CH-, or a compound of the formula:

$$R^6 - B$$

wherein R^6 is as defined in Claim 1 and B is a group of the formula:

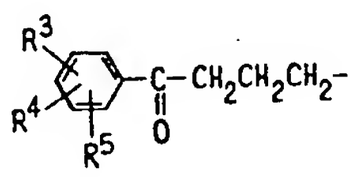
(wherein Z is as defined above) with a spiro amine derivative of the formula:



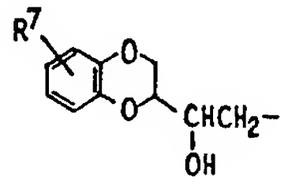
wherein R^1, R^2 and W are each as defined in Claim 1, optionally followed by reduction of a carbonyl group, or by hydrolysis of a protected carbonyl group, and optionally salifying the resultant product.

13. A process according to Claim 12, wherein W is an oxygen atom.

14. A process according to Claim 12, wherein R is a group of the formula:



or



wherein R^3, R^4, R^5 and R^7 are each as defined in Claim 1.

15. A pharmaceutical composition comprising at least one compound of the formula (I), given and defined in Claim 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable diluent or carrier.

16. The compounds of the formula (I), given and defined in Claim 1 other than those claimed in Claims 6 to 11 which are specifically disclosed herein.

17. Processes according to Claim 12, for producing a spiro amine of the formula (I), given and defined in Claim 1, which processes are substantially as herein described and exemplified.

18. Spiro amines of the formula (I), given and defined in Claim 1, whenever produced by a process according to any of Claims 12 to 14 and 17.

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